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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,135	09/08/2000	Kazuko Hirabayashi	44342.011800	2368

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,135	HIRABAYASHI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/28/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/05 has been entered.

Claims 4, 5, 8, and 11 are pending.

Applicant's traversal, the cancellation of claims 6, 7, 9, and 10, and the amendment to claims 4 and 5 in paper filed on 7/28/05 is acknowledged and considered by the examiner.

Claim Objections

Applicant is advised that should claims 4 and 8 be found allowable, claims 5 and 11 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 5, 8, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation '1 μg to 50 mg/human of poly (I);poly(C)' in instant claims 4 and 5 (and claims dependent therefrom) is not supported by the instant specification. There appears to be no written description of the limitation '1 μg to 50 mg/human of poly (I);poly(C)' in the application as filed. There is no page cited for support of the claims. See MPEP § 2163.06. The examiner thoroughly searched the instant specification and cannot found support for the limitation. Therefore, there is nothing in the specification that supports the methods as set forth in the claims.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

It is apparent that the applicants at the time the invention was made did not intend or contemplate using the methods cited in the claims as part of the disclosure of their invention. There is no evidence in the specification as filed that the applicants were in possession of the claimed methods as set forth in the claims 4, 5, and claims dependent therefrom, as it is now claimed, at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4, 5, 8, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "1 μg to 50 mg/human of poly (I);poly(C)" in claims 4, 5, 8, and 11 is a relative term which renders the claims indefinite. The term "1 μg to 50 mg/human of poly (I);poly(C)" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The limitation is not accepted terminology for a dosage because the dosage does not indicate if the term is administered per dose or in increments adding up to the concentrations set forth in the term.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desmyter et al. (Texas Reports on Biology and Medicine 35:516-522, 1977) taken with Yano et al., (YANO 1) (US Patent No. 5,298,614, cited on a prior PTO-892) and Bever et al. (Journal of Interferon Research, 5: 423-428, 1985) in further view of Liaw (J. Gastroenterol. Hepatol. 1997, 12:S346-53).

Desmyter teaches that interferon and interferon inducers (e.g., Poly IC) have been studied for treating hepatitis in a patient and chimpanzees (page 516). Desmyter teaches that Poly IC complexes with poly-L-lysine and carboxymethylcellulose were administered to chimpanzees that have a chronic hepatitis B infection (page 518). Two courses with the complexes were given to the chimps: 3mg/kg daily for one week and every other day for another week and, six month later, 3 mg/kg daily for 2 weeks and every other day for a total of 7 weeks (page 518). Both courses resulted in treatment of the hepatitis B infection (pages 518-519). Desmyter

teaches that the administration of Poly IC to the mammals results in direct action of interferon in the liver (page 519).

However, Desmyter does not specifically teach intravenously, hepatic intra-arterially, or transmucosally administering a complex comprising administering a cationic liposome with 1μg to 50 mg/man of poly IC, which has a mean length within the range of 100 to 500bp.

However, at the time the invention was made, YANO 1 teaches that poly I: poly C is a substance having interferon induction action and can be used for treating viral infections (abstract and column 3, lines 32-40). YANO 1 further teaches that the substance can be used as a pharmaceutical substance in humans (column 16). YANO 1 further teaches that when the chain length is limited to certain ranges, the resulting substance exhibit desired physiological activity with markedly less toxicity (column 4, lines 31-39). YANO 1 teaches that the fact that the control of molecular size of nucleic acid polymer within a specified range is the primarily important factor for remarkable reduction of toxicity of poly I: poly C and the preferred molecular size for using poly I: poly C is from 100 to 600 base numbers (column 11, lines 13-34). YANO 1 further teaches that the dsRNA can be delivered to an individual using different routes of delivery, including subcutaneous, intramuscular, or intravenous (column 18, line 32-46).

In addition, at the time invention was made, Bever teaches i.v. administration of 100 μg/kg Poly IC in humans, wherein the administration of Poly IC produced substantial levels of IFN (pages 86-89). Bever teaches that substantial levels of IFN were produced when Poly IC was administered weekly, biweekly and monthly (page 86). In addition, in view of the levels of IFN produced by administering Poly IC to a human taught by the prior art (e.g., Desmyter and

Bever), one of ordinary skill in the art would have reasonably expected that Poly IC could be used to treat hepatitis in a human with a reasonable expectation of success.

In addition, at the invention was made, Liaw teaches that interferon (IFN) is widely used for treating HBV, HCV, and HDV (page S346).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever and Liaw to treat hepatitis C in a human using intravenous or transmucosal administration of a complex comprising a cationic liposome with 1 μg to 50 mg/man of poly IC which has a mean length within the range of 100 to 500 bp; once, every day, every other day, weekly, or bi-weekly and inducing interferon chiefly in the liver in a human. One of ordinary skill in the art would have been motivated to use the complex for treating hepatitis C in a human because Poly IC was well known to one of ordinary skill in the art for inducing interferon in a patient for treating hepatitis.

In addition, one of ordinary skill in the art would have been motivated to use 3mg to 100 μg/man of Poly IC for treating hepatitis C in a human because the prior art teaches one of ordinary skill in the art that these concentrations of Poly IC would produce a sufficient amount of interferon *in vivo* to treat hepatitis in a human and one of ordinary skill in the art would make the necessary modifications to the concentration of Poly IC to practice the claimed method.

One of ordinary skill in the art would have been motivated to use intravenous or transmucosal administration to deliver the complex to treat hepatitis C in a human because the prior art teaches one of ordinary skill in the art that both routes of administration produce enough IFN to treat hepatitis in a human.

One of ordinary skill in the art would have been motivated, as a matter of designer choice, to deliver the complex once, every day, every other day, weekly, bi-weekly to treat hepatitis in a human because the prior art teaches one ordinary skill in the art that these regimens would produce enough IFN to treat hepatitis in a human.

One of ordinary skill in the art would have been motivated to use Poly IC which has a mean length within the range of 100 to 500bp of Poly IC as taught by YANO 1 for treating hepatitis in a human because this range displays reduced toxicity of the double stranded RNA in vivo.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/28/05 have been fully considered but they are not persuasive.

In response to applicant's argument that the amendment to claims 4 and 5 makes it clear that 3 mg/kg dosage of Desmyter does not fall within the range of the present claims, the argument is not found responsive because the limitation "1 ug to 50 mg/human of Poly IC" would be obvious because the range of concentration for treating hepatitis C using Poly IC was well known to one of ordinary skill in the art, at the time the invention was made. In view of the large amount of knowledge of using Poly IC to treat hepatitis provided in the prior art, one of ordinary skill in the art would make the necessary modifications to practice the claimed method.

In response to applicant's argument that new data suggesting that the complex according to the present invention can induce IFN chiefly in the liver of monkeys (Tables 1 and 2), the argument is persuasive, however, the argument supports statement in the 103 rejection that at the

time the invention was made, one of ordinary skill in the art would have reasonably expected that i.v. infusion of the complex would induce IFN chiefly in the liver.

In response to applicant's argument that Table 3 shows that the longer the average chain length of Poly I:C is, the more IFN-beta is induced and 500-600bp of Poly IC alone instead of the complex comprising even 100 ng/ml can hardy induce IFN, the argument is found persuasive, however, it is not apparent how this argument addresses the 103 rejection since either limitation was not rejected in the 103 rejection.

Claims 4, 5, 8, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desmyter et al. (Texas Reports on Biology and Medicine 35:516-522, 1977) taken with Yano et al., (YANO 1) (US Patent No. 5,298,614, cited on a prior PTO-892) and Bever et al. (Journal of Interferon Research, 5: 423-428, 1985) in further view of Liaw (J. Gastroenterol. Hepatol. 1997, 12:S346-53) as applied to claims 4 and 5 above, and further in view of YANO 2 (EP 06854557A1, IDS).

However, Desmyter, YANO 1, Bever, and Liaw do not specifically teach using the complex (2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid, e.g., lecithin) in the method.

However, at the time the invention was made, YANO 2 teaches using a complex (2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid, e.g., lecithin) to administer double stranded RNA to an individual and that using the lipid reduces toxicity of the double stranded RNA and improves the uptake efficiency of the double stranded RNA into cells

('457, abstract and pages 2-11). YANO 2 teaches that the complex can be delivered intravenously, intrarterially, locally, and rectally (page 16).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever and Liaw in further view of YANO 2 to use 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid (e.g., lecithin) with poly I:C in the method. One of ordinary skill in the art would have been motivated to use 2-O-(2-diethlaminoethyl)carbamoyl-1,3,-O-dioleoylglcerol and a phospholipid (e.g., lecithin) with poly I:C for treating hepatitis C in a human because the lipid reduces toxicity of the double stranded RNA in vivo and improves the uptake efficiency of the double stranded RNA into cells of the individual.

In addition, at the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to combine the teaching of Desmyter, YANO 1, Bever, and Liaw in further view of YANO 2 to use i.v., hepatic intra-arterial, or transmucosal administration of the complex to treat hepatitis C in a human. One of ordinary skill in the art would have been motivated to use the administration routes to deliver the complex to treat hepatitis in a human because the prior art teaches one of ordinary skill in the art that these routes of administration would produce enough IFN to treat hepatitis C in a human and these administration routes were well known to one of ordinary skill in the art for delivering Poly IC to a mammal. In addition, one of ordinary skill in the art would have been motivated to use hepatic intra-arterial administration because hepatitis results in the inflammation of the liver and one of ordinary skill in the art would determine that the liver would be the target area for inducing interferon using Poly IC.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/28/05 have been fully considered but they are not persuasive for the reasons set forth under the previous 103 rejection.

Response to Arguments

Applicant's arguments, see page 1, filed 7/28/05, with respect to 112 first paragraph new matter have been fully considered and are persuasive. The rejection of claims 5, 10 and 11 has been withdrawn because the amendment to claim 5 and the cancellation of claim 10.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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